through Applicants' Specification.

The Double Patenting Rejection

The Examiner has rejected claim 19 under 35 U.S.C. § 101 as claiming the same invention of that of claim 1 of prior U.S. Patent No. 5,591,629.

The Examiner has provisionally rejected claims 1-4, 9-14 and 19 under 35 U.S.C. § 101 as claiming the same invention of that of claims 1-4, 9-14 and 19 of copending application Serial No. 08/779,784 (the "'784 Application"). Applicants acknowledge this rejection and recognize it as provisional at present. The issue will be readdressed by Applicants at such time as other patentability issues are settled. Applicants further point out that claims 1-4, 9-14 and 19 have been subject to restriction and represent presently non-elected claims in the copending '784 Application.

The Examiner's § 101 Rejection

The Examiner has rejected Claim 19 under 35 U.S.C. 101 because the claim recites "natural autoantibody" and asserts that thus the claim is directed to non-statutory subject matter. Applicants have amended Claims 1, 9 and 19 to recite "isolated autoantibody", which is clearly not a product of nature by virtue of its being isolated. In view of this amendment, Applicants assert that this rejection is overcome and request it be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner has rejected claims 1-4, 10-14 and 19 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention. The Examiner asserts that these claims are rendered indefinite in the use of the term "active fragment thereof". Claims 1, 9 and 19 have been amended to recite "antigen binding fragment thereof", as suggested by the Examiner.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's rejection is obviated and should be withdrawn.

The Specification Enables the Claimed Invention

The Examiner has rejected claims 1-4, 9-14 and 19 under 35 U.S.C. 112, first paragraph alleging that the specification, while being enabled for methods of stimulating remyelination in mice does not reasonably provide enablement for methods of stimulating remyelination in humans or treatment of a demyelinating disease in mice or humans. The Examiner points out various aspects to this rejection, each of which will be addressed by Applicants below.

The Specification Enables Best Mode

The Examiner asserts that, as to claims 1-4. 9-14 and 19, the specification lacks complete deposit information for the deposit of SCH94.03, SCH79.08, O1, O4, A2B5 and HNK-1 and that it is not clear that cell lines producing the monoclonal antibodies possessing the properties of these antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation. Applicants respectfully disagree and submit that each of antibodies SCH94.03, SCH79.08, O1, O4, A2B5 and HNK-1 are known and publicly available.

With respect to SCH94.03 and SCH79.08, the Examiner contends that "Applicant's referral to the deposit of the hybridoma cell lines SCH94.03, SCH79.08 on pages 2-3 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR § 1.801-1.809 have been met". Applicants respectfully disagree and point out that on page 2, lines 29-33 and page 3, lines 1-2 in the specification, these antibodies are identified by their ATCC designated numbers and as being deposited under the terms of the Budapest Treaty. To further demonstrate this, copies of the ATCC facsimile receipts confirming the Budapest Treaty deposits and ATCC number designations of these antibodies are attached as Exhibit A.

With respect to antibodies O1 and O4, Applicants point out that on page 57 of the specification, lines 3-5, it is stated that

> O1 and O4 hybridomas were the gift of Dr. S.E. Pfeiffer (University of Connecticut, Farmington, CT).

The O1 and O4 antibodies are known and publicly available on request from Dr. S.E. Pfeiffer.

With respect to antibodies A2B5 and HNK-1, Applicants point out that on page 57 of the specification, lines 1-3, it is stated that

> A2B5, HNK-1, and XXMEN-OE5 (anti-bacterial lipopolysaccharide) hybridomas were purchased from American Type Culture Collection (Rockville, MD).

That these antibodies are indeed readily available from the ATCC is confirmed and demonstrated by photocopied pages of the ATCC Catalogue of Cell Lines and Hybridomas (Seventh Edition, 1992) (attached hereto as Exhibit B), which lists HNK-1 (ATCC TIB 200) and A2B5 (ATCC CRL 1520) available for purchase.

The Specification Enables The Claimed Methods

As to claims 1-4 and 9-14, the Examiner argues that the specification is not enabled for stimulating remyelination of CNS axons or treatment of demyelinating disease of the CNS in any mammal with the exception of a mouse. The Examiner states that "the prior art establishes that for demyelinating diseases in general, the currently employed mouse models of the specification (Experimental Autoimmune Encephalitis and Theiler's Virus-Induced Demyelinating Disease) do not predictably and reproducibly correlate with therapeutic effectiveness in the human species" and then cites publications in support of her argument. Applicants respectfully disagree.

Applicants assert that EAE (and, similarly, the model Theiler's Virus-Induced Demyelinating Disease) represents a well established and widely utilized model for *in vivo* testing of potential therapies for stimulating remyelination and treating demyelinating diseases in humans. Applicants respectively bring to the Examiner's attention, Section 2164.01(b) of the MPEP, wherein it is stated:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher* 427 F.2nd 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicants submit that demonstrated results showing stimulation of remyelination *in vivo* in

both mouse EAE and Theiler's Virus-Induced Demyelinating Disease models provide reasonable correlation to stimulating remyelination of CNS axons and treatment of demyelinating disease in mammals other than mice. Applicants note the Examiner's own admission on page 8 of the office action that taken in context, the teachings of Alvord et al. and Trautgott et al "suggest that the EAE model is the best model currently available for studying potential therapies for MS". The Examiner cites Raines as teaching that Experimental Autoimmune Encephalitis (EAE) lacks sufficient correlation with human disease and quotes from Raines, page 430, second column, middle of page. In fact, Raines himself, in the same paragraph and just following the Examiner's quote, teaches the following: "The **above discrepancies notwithstanding**, it has become clear that the closest picture to multiple sclerosis has emanated from the above immunological methods and this has served as incentive for the analysis of immunological and pathological events and therapeutic approaches pertinent to the multiple sclerosis problem"(emphasis added).

The standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention is undue or unreasonable. While some experimentation to test the claimed autoantibodies as therapies for demyelinating diseases such as multiple sclerosis in humans is necessary, such experimentation would utilize standard skills and would not constitute undue experimentation. With regard to the determination of what is undue experimentation, the PTO and the courts have commented that "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP § 2164.01, *citing M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether experimentation is necessary, but whether or not it is undue. *Ibid, citing In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Factors to consider in determining undue experimentation include (1) the quantity (time and expense) of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; (8) and the breadth of the claims. *Ibid, citing In re Wands*, 858 F.2d 731, 8 USPQ2d 1400

(Fed. Cir. 1988). In the present instance: (1) the quantity of experimentation, while significant, is not undue for the skilled artisan -the design and completion of clinical studies based on the *in vivo* model results would be standard procedure for those skilled in the art; (2) the direction or guidance provided by the specification is sufficient for the skilled artisan and appropriate for the time; (3) working examples are provided; (4) the nature of the invention, including, but not limited to *in vitro* studies and *in vivo* results from two distinct animal models; (5) the extent of prior art available to those skilled in the art with regard to testing potential such therapies; (6) the relative skill of those in the art is substantial; (7) the success of *in vivo* studies described in the specification enhance the predictability and provide reasonable correlation to stimulating remyelination of CNS axons and treatment of demyelinating disease in mammals other than mice; and (8) the breadth of the claims is commensurate with the significant skill of those in the art and the reasonable correlation provided in the demonstrated *in vivo* activity in mouse models. In view of the foregoing, Applicants submit that given the guidance and evidence provided by the specification, the established criteria for testing potential therapies in mammals other than mice, and the significant level of skill in the art a person of ordinary skill in the art could, without undue experimentation, test the claimed autoantibodies as stimulating remyelination and as therapies for demyelinating diseases, such as multiple sclerosis, in mammals other than mice.

The Examiner further asserts that the specification is not enabled for the pharmaceutical use of monoclonal antibodies O1, O4, A2B5, HNK-1 and natural or synthetic autoantibodies having the characteristics thereof. The Examiner also states that "Applicant clearly teaches that the aforementioned antibodies have different antigen binding specificities (page 10) and are encoded by different germline genes and thus do not possess the characteristics of SCH94.03 and SCH94.32". Applicants concur that O1, O4, A2B5 and HNK-1 are encoded by different germline genes, although they, like SCH94.03 and SCH94.32, are germline encoded. Applicants submit, however, that O1, O4, A2B5 and HNK-1 are like SCH94.03 and SCH94.32 in their characteristic of stimulating demyelination and being suitable for treatment of demyelinating disease. A copy of a submitted publication detailing research studies completed by Applicants entitled "Targeting of IgMK Antibodies to Oligodendrocytes Promotes

Central Nervous System Remyelination" is attached as Exhibit C. This submitted publication evaluates SCH79.08, O1, O4, A2B5 and HNK-1 and demonstrates the ability of these antibodies, each with distinct antigen specificities, to promote CNS remyelination in a Theiler's Virus-Induced Demyelinating Disease mouse model. Thus, despite distinct antigen specificities (although they all bind to oligodendrocyte-associated antigens), SCH94.03, SCH94.32, SCH79.08, O1, O4, A2B5 and HNK-1 all possess remyelination promoting activity.

In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph is overcome and should be withdrawn.

The Claimed Invention is Entitled to the Earliest Date of Priority

The Examiner asserts that benefit **can not** be granted back to Applicant's claimed benefit of priority to the parent application, now U.S. Patent 5,591,629, filed April 29, 1994 (the '629 Patent). Specifically, the Examiner states that "the scope of the instant claims in regard to 'mammal' and monoclonal antibodies was not enabled in the parent application". Applicants respectively disagree. The '629 Patent details the generation and selection of spinal cord homogenate (SCH) monoclonal antibodies to promote CNS remyelination. The '629 Patent further teaches that administration of the antibody SCH94.03 was found to promote central nervous system remyelination, and therefore inherently treat demyelinating disease, in mice chronically infected with Theiler's murine encephalomyelitis virus. Methods of employing these, and other remyelination-promoting antibodies, in stimulating remyelination and treating demyelinating diseases are provided in the specification of the '629 at pages 12-14. In particular, on page 13, lines 30-42, of the '629 Patent it is stated:

> The effectiveness of the amount of the monoclonal antibody being administered can be assessed using any number of clinical criteria, for example, as described in Example 3, including overall appearance of the mammal, the activity of the mammal and the extent of paralysis of the mammal. The effectiveness of the amount of monoclonal antibody necessary to induce remyelination in humans can also be assessed in a double blinded controlled trial. Patients with fixed neurological deficits from demyelinating disease can be treated with monoclonal antibody or controls. Improvement in isometric muscle

strength as detected by quantitative biomechanics muscle testing could be used as the primary therapeutic end-point.

In fact, the instant application and priority application are commensurate in scope as to this aspect of the invention. In view of the foregoing remarks, Applicants submit that the Examiner's rejection of Applicant's claimed benefit of priority is overcome and should be withdrawn.

The Examiner's § 102(b) Rejections

The Examiner has rejected claim 19 under 35 U.S.C 102(b) as being anticipated by Kasei et al with respect to the antibody A2B5. The Examiner has rejected claim 19 under 35 U.S.C 102(b) as being anticipated by Gard et al with respect to the antibodies A2B5, O1 and O4. The Examiner has rejected claim 19 under 35 U.S.C 102(b) as being anticipated by Fredman et al with respect to the antibody A2B5. The Examiner has rejected claim 19 under 35 U.S.C 102(b) as being anticipated by Eisenbarth et al with respect to the antibody A2B5. The Examiner has rejected claim 19 under 35 U.S.C 102(b) as being anticipated by Bansal et al with respect to the antibodies O1 and O4. Applicants have amended claim 19 to delete pharmaceutical compositions of A2B5, O1 and O4. In view of the amendment to claim 19, Applicants assert that this rejection should be withdrawn.

The Examiner has rejected claims 1-4, 9 and 11-14 under 35 U.S.C 102(b) as being anticipated by Miller et al. The Examiner argues that Miller et al teaches that administration of the antibody SCH94.03 was found to promote central nervous system remyelination and therefore inherently treat demyelinating disease in mice chronically infected with Theiler's murine encephalomyelitis virus. Miller et al is a paper authored by Applicants and others, published in the October 1994 issue of The Journal of Neuroscience. Applicants remind the Examiner that the instant application claims priority under 35 U.S.C. 120 to USSN 08/236,520, now issued patent #5,591,629 ("the '629 Patent"), filed April 29, 1994, prior to the publication of Miller et al. Applicants further point out that the '629 Patent fully incorporates the data and teaching of Miller et al. In view of this, Applicants request that the rejection under 102(b) as anticipated by Miller et

al be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

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